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PATENT

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1/18/05
Date

Michelle Hobson
Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: Jeffrey N. Fredman
WOLFFE et al.	Group Art Unit: 1634
Serial No.: 09/844,501	Confirmation No.: 9055
Filing Date: April 27, 2001	Customer No.: 20855
Title: DATABASES OF REGULATORY SEQUENCES; METHODS OF MAKING AND USING SAME	

TRANSMITTAL LETTER

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

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x Reply to Examiner's Answer (17 pages) *in triplicate*

x Return receipt postcard.

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Total Claims	30	- 122	0	x \$50.00	\$0
Independent Claims	2	- 22	0	x \$200.00	\$0
Multiple dependent claims not previously presented, add \$360.00					\$0
Total Amendment Fee					\$0
Small Entity Reduction (if applicable)					\$0
TOTAL FEE DUE					\$0

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Respectfully submitted,

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A.P. Wolffe *et al.*

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SEQUENCES; METHODS OF
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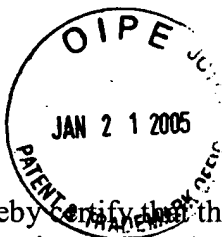
Group Art Unit: 1637

Confirmation No.: 9055

REPLY TO EXAMINER'S ANSWER

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Sir:

INTRODUCTION

Appellants submit this reply brief on appeal in accordance with 37 C.F.R. § 1.193(b)(1). An Examiner's Answer was mailed on November 17, 2004. In light of the record in this case and following remarks, Appellants respectfully request that the decision of the Examiner be reversed.

REMARKS

The Examiner has maintained the rejections of all pending claims as allegedly obvious over U.S. Patent No. 5,635,355 ("Grosveld") alone or in view of the NEB catalog, U.S. Patent No. 5,500,356 ("Li") or U.S. Patent No. 6,444,421 ("Chung") under 35 U.S.C. § 103(a).

For the reasons of record and those previously set forth in the Appellants' Brief on Appeal, the claims on appeal are patentable over the combination of cited references because there is no teaching, suggestion or motivation within these references to support the assertions made by the Examiner. No reference alone, nor any combination of any of these references would result in the claimed methods.

Appellants address the issues raised in the Examiner's Answer in turn below.

1. Statement of the Issue

The Examiner's Answer stated that the issue is whether "intrinsic evidence provided by the express broad definition of the claim term 'library' in the specification supports the reasonable interpretation that the Grosveld references teaches a 'library' within the scope of the claimed invention." (Examiner's Answer, page 10)

The Examiner's statement of the issue is not accurate. The issue remains whether the claims, when properly construed, are obvious over Grosveld. For the reasons of record and reiterated herein, Appellants again submit that Grosveld fails to render the claims obvious.

The Examiner has constructed a rather tortuous obviousness argument that is based on a picking and choosing of various portions of Grosveld's disclosure, combined with a strained definition of the term "library" as encompassing a single sequence. However, regardless of the definition of the term "library," the record shows that no motivation exists for one of skill in the art to combine the teachings from Grosveld in the way that has been set forth by the Examiner; moreover, said combination fails to suggest the claimed methods. Thus the *prima facie* assertion of obviousness fails. See Section 2 below.

Furthermore, and again contrary to the Examiner's assertions, Appellants have provided evidence that their use of the term "library" is consistent with its ordinary meaning in the art, and that the specification shows no intent of the part of Appellants to impart a novel meaning, or one contrary to its normal meaning in the art, to the term. *See* Section 3. Appellants have also provided evidence establishing that the Examiner's attempted definition of the term is inconsistent with its ordinary meaning in the art. *See* Section 3.

2. Prima Facie Case

The Examiner maintained that Appellants did "not dispute that Grosveld teaches the steps as illustrated." (Examiner's Answer, page 10). In support of this assertion, the Examiner's Answer states, on page 10:

Grosveld teaches each and every limitation of the invention of claim 123, with elements (a)-(d) of claim 123 found in column 8, lines 1-25 and elements (e)-(f) found in column 15, lines 43-47 and in claim 1 at column 21. ...

While the Appellant disputes the prima facie case, the Appellant does not dispute that Grosveld teaches the steps as illustrated. What Appellant does dispute is whether Grosveld meets the preamble limitation that a "library" is prepared.

In fact, Appellant has consistently and strongly disputed the assertion that Grosveld teaches the steps of independent claim 123. Indeed, Appellants have previously pointed out that the fragments cloned by Grosveld are different from the fragments cloned in the claimed method. Whereas the fragments cloned by Grosveld are individual purified fragments containing a DNase hypersensitive site within the fragment (*see* Grosveld at column 15, for example), an entire genome's worth of DNA is cleaved in the claims at issue. *See, e.g.,* independent claim 123, which recites the provision of a cell nucleus [step (a)] and contact of the nucleus with a first enzyme; [step (b)]¹ and the resulting collection of genomic DNA fragments [step (d)] is subjected to a cloning step [step (e)] such that fragments containing one end defined by cleavage with the first

¹ Note also that the claims do not require that the first enzyme be DNase I (*see, e.g.,* claim 127) and therefore are not restricted to cleavage at DNase hypersensitive sites.

enzyme are selectively cloned. *See, also*, Response filed December 17, 2003, resubmitted February 26, 2004.

Above and beyond the fact that the portions of Grosveld's disclosure chosen by the Examiner do not suggest the claimed methods, no plausible motivation for their combination has been advanced. The Examiner has alleged that Grosveld provides the motivation because the reference discloses ligation into a vector of fragments that had previously been characterized as containing DNase I hypersensitive sites, and because such vectors can be used to provide integration site-independent expression of a transgene that is present in the same vector. *See*, for example, Office Action of September 29, 2003, page 6. However, the combination of Grosveld's identification of DNase hypersensitive sites, and their use in a vector containing a transgene to obtain site-independent expression of the transgene after random integration of said vector into a genome, in no way suggests a method for obtaining a collection of regulatory sequences by selective cloning of enzymatically-cleaved genomic DNA, as claimed.

Faced with a similar issue (namely, an obviousness rejection based on a number of statements from a single reference), in *In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313 (CAFC 2000), the Federal Circuit reversed the finding of obviousness. In reversing, the Federal Circuit held that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims cannot be predicated on mere identification in a reference of individual components of claimed limitations. *Kotzab*, 55 USPQ2d at 1316-1317. Indeed, the Court specified that particular findings must be presented as to why a skilled artisan, with no knowledge of the claimed invention, would have selected those components for combination in the manner claimed. *Id.* The Federal Circuit also stated that mere identification of prior art statements that, in the abstract, appeared to suggest claimed limitations does not establish a *prima facie* case of obviousness without a finding as to a specific understanding or principle within the knowledge of the skilled artisan that would have motivated one with no knowledge of the invention to make the combination in the manner claimed (*In re Kotzab*, 55 USPQ2d at 1317):

While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two

statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection cannot be predicated on the mere identification [in the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

Applying the law as set forth by the Court in *Kotzab*, Appellants note that Grosveld's disclosure is directed to construction of vectors, comprising a gene sequence, to be used for transfection of mammalian cells and integration into the genome of said cells, so as to obtain expression of the gene. *See* Grosveld Abstract (cover page) and "Field of the Invention" (Column 1). The Examiner has not explained how, in this context, one of skill in the art would be led to pick and choose those portions of Grosveld's disclosure that the Examiner alleges would lead to the presently-claimed methods for obtaining collections of regulatory sequences. As such, the obviousness rejection is unsustainable.

Furthermore, the obviousness rejection cannot be maintained because the Examiner has failed to identify a specific understanding or principle within the knowledge of the skilled artisan that would have motivated him or her to combine the various teachings scattered throughout Grosveld's disclosure in a way that would arrive at the claimed subject matter. Although the teachings selected by the Examiner from Grosveld's disclosure may have appeared to him to suggest the claimed methods, it is only with Appellant's invention in hand that he was able to make such a combination, and the rejection is, therefore, an impermissible hindsight reconstruction of the claimed methods. *See In re Kotzab* 55 USPQ2d 1313, 1318 (Fed. Cir. 2000).

Thus, for the reasons of record, Appellants reiterate that no combination of teachings from Grosveld suggest the methods set forth in the claims on appeal, nor has the Examiner identified any motivation for one of skill in the art to combine the teachings the Examiner has selected to arrived at the claimed methods. Accordingly, a *prima facie* case of obviousness has not been and cannot be established based on Grosveld.

3. Intrinsic Evidence

The Examiner also cites case law in an attempt to support the assertion that the intrinsic evidence of the specification is always determinative of the meaning of a claim term. From the cited cases, the following conclusions appear to be drawn: (1) that the normal meaning of the term "library" in the art of molecular biology does not apply to the pending claims and (2) that Appellants' description of the term "library" on page 46 is not subject to any interpretation, either by other portions of the specification or by documents available at the time of filing. (Examiner's Answer, page 11). With regard to the second assertion, it is also maintained, seemingly on the grounds that the single sentence on page 46 must be viewed in isolation of the rest of the specification and state of the art, that this sentence somehow requires the interpretation that DNA libraries as claimed may include clones containing one or more copies of the same sequence. This assertion has lead the Examiner to, summarily and repeatedly, reject Appellant's argument that the normal and customary use of the term "library" in the field of molecular biology refers to collections of multiple, different fragments of DNA.

(a) Normal meaning of the term in the art supercedes intrinsic evidence

As an initial matter, Appellants traverse the Examiner's assertion that the specification is the primary source for determining the meaning of claim terms. To the contrary, the primary determinant of the meaning of a claim term is, and always has been, the normal meaning of the term in the art. *See, for example, Moba, B.V. et al. v. Diamond Automation, Inc.*, 66 USPQ2d 1429, 1433 (Fed. Cir. 2001):

As a general rule, claim language is given the ordinary meaning of the words in the normal usage of the field of the invention. [Citing *Toro Co. v. White Consol. Indus.*, 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999).]

Indeed, even one of the very cases cited by the Examiner in the Examiner's Answer, cautions against ignoring the ordinary and customary meaning of a claim term:

Consulting the written description and prosecution history as a threshold step in the claim construction process, before any effort is made to discern the ordinary and customary meanings attributed

to the words themselves, invites a violation of our precedent counseling against importing limitations into the claims. *Texas Digital Systems, Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 64 USPQ2d 1812, 1819 (Fed. Cir. 2002), *cert. denied*, 538 U.S. 1058 (2003)

Thus, the Federal Circuit has repeatedly cautioned against importing limitations into the claims by failing to consult the file history to determine the ordinary meaning of the claim.

In the pending case, the Office has ignored these cautions and instead has artificially broadened the claim term "library" by ignoring its ordinary and customary meaning, based on an isolated selection from the specification. In light of a record that clearly shows that the ordinary meaning of the term "library" in the art of molecular biology does not include a collection of identical molecules, the Examiner's interpretation of this claim term is improper. *See*, for example, Appendix B attached to the Appeal Brief dated September 30, 2004, in which a library is defined as "a large number of recombinant DNA clones, *each one of which contains a different segment of foreign DNA.*" (emphasis added).

Thus, the Examiner has failed to recognize the normal meaning of the term to the skilled artisan and, as a result, has incorrectly construed the claim.

(b) Appellants definition is not contrary to normal and customary meaning of the term "library"

Appellants also strongly dispute the Examiner's contention that the so-called "definition" of the term library on page 46 of the specification should be viewed in isolation from the rest of the specification. In fact, the specification can be used to define the meaning of a claim term if applicant, serving as his or her own lexicographer, has provided a new definition, or one that is different from the customary meaning of the term in the art. *See*, for example, *Brookhill Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1300, 67 USPQ2d 1132, 1136 (Fed. Cir. 2003):

The presumption [of ordinary and customary meaning of a claim term] will be overcome where the patentee, acting as his or her own lexicographer, has clearly set forth a definition of the term different from its ordinary and customary meaning. [Citing *in re*

Paulsen, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994); *Intellical, Inc. v. Phonometrics, Inc.*, 952 F.2d 1384, 1387-88, 21 USPQ2d 1383, 1386 (Fed. Cir. 1992)]

In the pending case, the Examiner has improperly fastens upon Appellant's statement at page 46 of the specification to support an assertion that the term "library" has been re-defined by applicants. However, this statement² is in fact entirely consistent with the art-recognized meaning of the term "library." Moreover, numerous other portions of the specification use the term "library" in a manner consistent with its normal and customary meaning in the art of molecular biology (*i.e.*, a collection of different sequences), for example:

- page 28, lines 6-7: "Isolated polynucleotide *fragments* corresponding to *accessible regions* can be cloned and used to prepare *collections or libraries* of accessible regions." (emphases added, note use of the plural and note equivalence of the terms "collections" and "libraries")
- page 38, lines 21-23: ". . . the isolated *fragments* can be cloned to generate a library of regulatory *sequences*. The *nucleotide sequences* of the *members of the library* can be determined . . ." (emphases added, note uses of the plural)
- page 45, lines 7-9: "*Collections* of *accessible region sequences* from a particular cell can be cloned to generate a library, and the *nucleotide sequences* of the *members of the library* can be determined . . ." (emphases added, note use of plural)³
- page 47, lines 5-6: "The libraries formed can represent *accessible regions* for a particular cell type or cellular condition." (emphasis added, note use of plural)⁴
- page 47, lines 15-17: "Determination of the *nucleotide sequences* of the *members of a library* can be used to generate a database of *accessible*

² that a library is a pool of DNA fragments that have been propagated in a cloning vector

³ Also presented in Appellants' Response dated May 18, 2004 at pp. 3-4.

⁴ Also presented in Appellants' Response dated May 18, 2004 at page 3

sequences specific to a particular cell type." (emphases added, note use of plural)

Moreover, the working examples provided in the specification show libraries containing different sequences. *See* Example 15, pp. 112-116 and SEQ ID NOS. 10, 11 and 12.

Given that the specification makes clear throughout that the claimed libraries necessarily include "collections" of "accessible region sequences" and are libraries in which the "nucleotide sequences" of the "members of the library" can be determined, it is unclear to Appellants how the such libraries could, under any circumstances, consist of identical sequences, as asserted by the Examiner.

In sum, Appellants again note that, even if the normal and customary meaning of the term "library" in the art of molecular biology is disregarded, as the Examiner appears to have done, the intrinsic evidence of the specification is all that is necessary in order to properly construe the term "library" to refer to clones of multiple, different DNA sequences. Moreover, nothing in the specification indicates that Appellants intended a definition of library different from its normal and customary meaning in the art of molecular biology.

(c) Intrinsic evidence not limited to specification

Furthermore, the Examiner's insistence on the specification as the sole source of intrinsic evidence is misplaced. Rather, the intrinsic evidence, as pointed out in one of the cases cited on page 11 of the Examiner's Answer, includes **both** the specification and the file history:

The intrinsic record includes the specification and the file history. [Citing *Masco Corp. v. United States*, 303 F3d 1316, 1324 (Fed. Cir. 2002)] *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 73 USPQ2d 1011 (Fed. Cir. 2004).

In the case at hand, the file history has made it abundantly clear that the claimed methods generate nucleic acid libraries composed of a collection of different nucleotide sequences. *See* Response dated December 17, 2003 (Resubmitted February 26, 2004) at pp. 6-8; Response dated May 18, 2004 at pp. 2-3 and Exhibits A and B attached to

Response dated May 18, 2004; Response dated June 16, 2004 at p. 6 and Appeal Brief dated September 30, 2004 at pp.12-14 and Appendices B and C attached to Appeal Brief.⁵

Thus, it is improper and incorrect for the Examiner to assert: (1) that the intrinsic evidence supports his proposed definition of the term “library” to include a clone and (2) that Grosveld teaches a method which prepares libraries as claimed. *Examiner’s Answer*, page 13.

(d) Claim term must be taken in context

Moreover, the meaning of a claim term must be taken within the context of the claim itself:

. . . the context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those terms. [Citing *Hockerson-Halberstadt, Inc. v. Converse, Inc.*, 183 F.3d 1369, 1374, 51 USPQ2d 1518, 1522 (Fed. Cir. 1999)] *Brookhill Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1300, 67 USPQ2d 1132, 1136 (Fed. Cir. 2003)

The words used in the claims must be considered in context and are examined through the viewing glass of a person skilled in the art. *Ferguson Beauregard/Logic Controls, Division of Dover Resources, Inc. v. Delaware Capital Formation, Inc.*, 69 USPQ2d 1001, 1009 (Fed. Cir. 2003)

Moreover, as this court has repeatedly counseled, the best indicator of claim meaning is its usage in context as understood by one of skill in the art at the time of invention. [Citing *Markman*, 52 F.3d at 986.] *Moba, B.V. et al. v. Diamond Automation, Inc.*, 66 USPQ2d 1429, 1435 (Fed. Cir. 2001)

In the present case, the claims recite contacting a cell nucleus (comprising cellular chromatin) with an enzyme (claim 123) or a probe (claim 143) which reacts with accessible regions. It is well-known to those of skill in the art that cellular chromatin contains a plurality of accessible regions. *See, for example, Gross et al. (1988) Ann. Rev. Biochem. 57:159-197*, wherein the following statements are made:

⁵ For that matter, the specification also discloses a library containing multiple different nucleic acid sequences. *See Example 15 at pp. 112-116, including SEQ ID Nos. 10, 11 and 12.*

These accessible regions are operationally defined by their pronounced sensitivity to nuclease cleavage or chemical modification . . .

Hypersensitive sites generally represent a minor (ca. 1%), but highly selective fraction of the genome.

. . . the sites themselves most often encompass a unit length close to that of the nucleosomal repeat (ca. 200 bp) or several multiples thereof . . .

(All quotes taken from Gross *et al.* p.160)

Applying the information provided by Gross to a mammalian genome of ca. 3×10^9 base pairs, 1% of such a genome would contain 3×10^7 base pairs. If each accessible region were 200 nucleotides in length, a total of $3 \times 10^7 / 2 \times 10^2 = 1.5 \times 10^5$ accessible regions are present. Thus, in an average mammalian genome, 150,001 fragments would be produced by an enzyme that cleaves accessible regions. These 150,001 fragments are then subjected to further fragmentation. *See* claim 123, step (c); claim 143, step(b). It should therefore be clear that, in the context of the claims, one of skill in the art of molecular biology would realize that over 150,001 fragments are produced when the claimed method is practiced with a typical mammalian genome. It should also be clear that, even for smaller genomes, multiple fragments will be produced.

Consequently, it is not reasonable to assert, as the Examiner has done, that a library according to the claims could consist solely multiple copies of the same sequence.

(e) Examiner's proposed definition of "library" is repugnant to its normal meaning in the art

Finally, the definition of "library" propounded by the Examiner is not only contrary to the normal and customary meaning of the term in the art, it is actually repugnant to that meaning. One or more nucleic acid sequences propagated in a vector molecule is denoted a "clone" in the art of molecular biology; a collection of clones having different inserts⁶ is denoted a "library." *See*, for example, Appendix B attached to

⁶ Such as might be obtained, for example, by: (1) cleaving genomic DNA with a restriction enzyme and cloning the resulting collection of fragments to generate what is known in the art as a "genomic library" or

the Appeal Brief dated September 30, 2004, in which a library is defined as “a large number of recombinant DNA clones, each one of which contains a different segment of foreign DNA.” Immeasurable confusion would rage in the field of molecular biology if these two terms were mistakenly intermixed, as has been done by the Examiner. To refer to a single clone as a library, based on the presence of multiple identical copies of the clone in a sample, as the Examiner has done, is akin to identifying a building containing one million copies of the same book as a library.

Thus, the Examiner has improperly and incorrectly re-defined the term “library” to the point that the term has been removed so far from its normal and customary meaning as to be essentially meaningless.

(f) The record as a Whole supports Appellants’ claim construction and refutes Examiner’s

Appellants have shown that the normal and customary use of the term “library” in the art of molecular biology is consistent with their use of that term in the specification and claims. They have further shown that a proper consideration of the intrinsic evidence, including both the specification and the file history, does not reveal any attempt to contradict or somehow re-define this normal and customary. The various art definitions provided by Appellants, which have been dismissed by the Examiner, constitute additional intrinsic evidence supporting Appellants’ interpretation of the claim language, inasmuch as they are of record and are part of the file history. These art-recognized definitions are not, in any way, inconsistent with the specification's definition of the term “library.” Rather, they entirely supports Appellants’ interpretation that a library contains clones of different DNA sequences.

Therefore, when properly interpreted, the claims are drawn to methods of making DNA libraries in which the sequences making up the library are different. Furthermore, under this accurate interpretation, it is clear that the claims are nonobvious over Grosveld.

(2) reverse transcribing a population of mRNA molecules and cloning the resultant pool of DNA molecules to generate what is known in the art as a “cDNA library”

4. Preamble

After asserting on page 10 that the only issue relates to intrinsic evidence, the Examiner then maintains, on page 13, that a "second issue is whether the preamble limitation of 'library' constitutes a structural limitation on the method claim." (Examiner's Answer, page 13).

For the reasons noted above, the steps of the claims on appeal are different from Grosveld whether or not the term "library" is included in the preamble.

Appellants also note that they were not allowed to put language into the claims positively reciting that the plurality of sequences of the clones are different from each other. *See*, Supplemental Amendment filed June 16, 2004. Inasmuch as the Examiner was on record as asserting that the claimed methods included both libraries containing multiple sequences and libraries containing a single sequence (Office Action of September 29, 2003 at page 2; Office Action of April 13, 2004 at pp. 9-10; Advisory Action of June 2, 2004), it was believed that this amendment represented a narrowing of the claim and would simplify issues for appeal.

Despite the Examiner's express encouragement to submit this supplemental amendment, and the clear support in the specification as filed (*e.g.*, working examples), entry thereof was refused. *See* Advisory Action dated June 29, 2004. Appellant submits that the Examiner's refusal to enter the amendments, especially after encouraging Appellant to make them, has resulted in unnecessary delays and expense, particularly in the form of this Appeal process. Appellant's good faith attempt to avoid the Appeal process by amending the claims to make explicit what was originally implicit was improperly denied by the Examiner and would obviate any remaining issues.

In support of the refusal to enter the amendments, the Advisory Action simply stated "The arguments are not considered since they relate to the amendment which was not entered." Accordingly, Appellants remain unaware of why the amendments initially encouraged by the Examiner were subsequently not entered.

5. Library Motivation

Finally, the Examiner's Answer asserts again that Grosveld teaches the "manipulative steps" of the claims and points to a paper regarding cosmid libraries cited at col. 13, lines 56-58 of Grosveld. (Examiner's Answer, pages 14-15). The Examiner's Answer also cited MPEP 2144 for the proposition that Grosveld need not contain the same motivation as the specification. *Id.*

The citation to MPEP 2144 cannot change the fact that Grosveld does not teach or suggest either the "manipulative steps" or the libraries themselves. For the reasons detailed above, Grosveld does not teach the methods of the claims on appeal and contains no motivation to alter the methods he does disclose to arrive at the claimed subject matter.

Moreover, the rule that the motivation need not be the same is irrelevant in this case. What is relevant is the well-settled case law clearly and consistently holding that there is no motivation to alter a reference where the proposed motivation would destroy the intended function of the reference, as set forth, for example in *In re Fritch* 23 USPQ2d 1780, 1783, n.12 (Fed. Cir. 1992) and *In re Ratti* 123 USPQ 349, 352 (CCPA 1979):

A proposed modification [is] inappropriate for an obviousness inquiry when the modification renders[s] the prior art reference inoperable for its intended purpose.

[I]t would require a substantial reconstruction and redesign of the elements shown in [a cited reference] as well as a change in the basic principles under which [that reference's] construction was designed to operate.

In sum, if the Office's efforts to attain the claimed subject cause the reference to become inoperable or destroy its intended function, then the requisite motivation to make the modification would not have existed.

Here, both the Grosveld references are directed to cloning of hypersite-encompassing fragments in order to prepare constructs used for gene integration. *See, e.g.,* Abstract and Examiner's Answer page 14, describing cosmids of Grosveld paper. Thus, the intended function of Grosveld is to make constructs in which a coding sequence

(gene) is linked to the fragments encompassing the hypersites. Modifying Grosveld as suggested by the Examiner to result in a library as claimed would completely destroy the sole intended function of Grosveld's constructs, at the least because Grosveld's constructs would not contain a coding sequence.

Thus, no matter what the Examiner alleges as the motivation to alter Grosveld to arrive at the claimed subject matter, such altering would: (1) result in a completely different process than that claimed and (2) fundamentally destroy the function of Grosveld's constructs. Accordingly, there is no motivation that can be used to justify the rejection and the Examiner's decision should be reversed.


CONCLUSION

For the reasons stated above, Appellant respectfully submits that the pending claims define subject matter that is nonobvious over the art cited by the Examiner.

Accordingly, Appellants request that the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

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